The impact of Connshing's syndrome - mild cortisol excess in primary aldosteronism drives diabetes risk

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The impact of *Connshing's* syndrome - mild cortisol excess in primary aldosteronism drives diabetes risk

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With great interest, we have read the recent study by Wu *et al.* [1]. By taking advantage of the Taiwan National Health Insurance database, the authors provide evidence that in patients with primary aldosteronism, treatment by adrenalectomy (ADX) significantly reduced the risk of new-onset diabetes mellitus (NODM) to the level observed in patients with essential hypertension. Significantly, patients receiving medical therapy of primary aldosteronism with mineralocorticoid receptor antagonist (MRA) had a significantly higher risk of diabetes than patients with essential hypertension. The authors suggest some potential explanations for these disparate results: Although ADX would normalize aldosterone hypersecretion levels shortly after surgery, MRA therapy could augment circulating aldosterone serum levels, which might be associated with deleterious nongenomic effects of aldosterone. Further explanations might include low long-term adherence to MRA therapy and a more pronounced effect on blood pressure control by ADX.

Although we agree that the proposed mechanisms may contribute to the observed difference of surgical and medical therapy on metabolic effects in primary aldosteronism patients, we would like to point out another potential explanation for this interesting epidemiological observation. We could recently demonstrate by a mass spectrometry-based analysis of the 24-h urine steroid metabolome in 174 patients with newly diagnosed primary aldosteronism that a significant proportion had mild glucocorticoid excess concurrently with excess production of aldosterone [2], a constellation we termed Connshing's syndrome. In our cohort, ADX resolved both mineralocorticoid and glucocorticoid excess and a proportion of around 30% of patients undergoing surgery even had evidence of postoperative adrenal insufficiency. Intratumor expression of the cortisol synthesis enzyme CYP11B1 was significantly associated with the corresponding in-vivo glucocorticoid excretion. In our patient cohort, several surrogate parameters of metabolic risk correlated significantly with glucocorticoid but not mineralocorticoid output. We proposed that, although ADX removed both mineralocorticoid and glucocorticoid excess, patients treated with MRA might have persistent metabolic risk, as the glucocorticoid excess remains unopposed.

This hypothesis is also supported by a recent cohort study in 2533 primary aldosteronism patients [3], published by the same group as the current report on NODM risk. That report found an ongoing increase in osteoporotic fracture risk in women with primary aldosteronism receiving treatment with MRA, whereas women who underwent surgical removal of their aldosterone-producing adrenal adenoma did not have an increased risk of osteoporosis.

Hypercortisolism, even if mild as in primary aldosteronism patients, is able to increase the risk for osteoporosis [4] and diabetes mellitus [5], whereas those risks are difficult to reconcile with aldosterone excess. Therefore, we propose that the correction of coexisting hypercortisolism by ADX will be the main reason for the improvement of NODM observed by Wu *et al.* [1]. This cannot be achieved by selective MRA therapy, with persistent adrenal cortisol excess driving the increased risk of NODM and osteoporosis.

Prospective randomized studies would be necessary to clarify whether patients with primary aldosteronism and evidence of Connshing's syndrome should receive additional glucocorticoid-opposing treatment when treated medically with MRA to efficiently counteract adverse metabolic risk.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Wu VC, Chueh SJ, Chen L, Chang CH, Hu YH, Lin YH, *et al.* Risk of new-onset diabetes mellitus in primary aldosteronism: a population study over 5 years. *J Hypertens* 2017; 35:1698–1708.
2. Arlt W, Lang K, Sitch AJ, Dietz AS, Rhayem Y, Bancos I, *et al.* Steroid metabolome analysis reveals prevalent glucocorticoid excess in primary aldosteronism. *JCI Insight* 2017; 2:93136.
3. Wu VC, Chang CH, Wang CY, Lin YH, Kao TW, Lin PC, *et al.* Risk of fracture in primary aldosteronism: a population-based cohort study. *J Bone Miner Res* 2017; 32:743–752.
4. Morelli V, Eller-Vainicher C, Salcuni AS, Coletti F, Iorio L, Muscogiuri G, *et al.* Risk of new vertebral fractures in patients with adrenal incidentaloma with and without subclinical hypercortisolism: a multicenter longitudinal study. *J Bone Miner Res* 2011; 26:1816–1821.
5. Di Dalmazi G, Vicennati V, Rinaldi E, Morselli-Labate AM, Giampalma E, Mosconi C, *et al.* Progressively increased patterns of subclinical cortisol hypersecretion in adrenal incidentalomas differently predict major metabolic and cardiovascular outcomes: a large cross-sectional study. *Eur J Endocrinol* 2012; 166:669–677.

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